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Miliary Tuberculosis in Adults

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Summary: Of 40 adults with miliary tuberculosis 24 had "overt" disease; in them miliary mottling was usually present on the chest radiograph, and tubercle bacilli were readily isolated from sputum, urine, or cerebrospinal fluid. In the remaining 16 patients the disease was termed "cryptic" because its usual clinical and radiographic features were absent. This cryptic type is as common as the overt type in patients over 60 years. In this series the peak age incidence was in the eighth decade, and possibly this increase in the incidence age is due to the breakdown of old tuberculous foci in patients with diminished immunological mechanisms.

Cryptic miliary tuberculosis is a difficult diagnostic problem and should be suspected in any elderly patient, particularly a woman, who has an unexplained pyrexia, pancytopenia, or leukaemoid reaction. In 10 cases it was diagnosed by a therapeutic trial with para-aminosalicylic acid and isoniazid, a fall of temperature to normal (usually within a week), weight gain, a rise in haemoglobin, and increased well-being being the criteria of improvement. The use of such a trial is strongly advocated as a specific method of diagnosing cryptic miliary tuberculosis.

Introduction

In its common form miliary tuberculosis is a disease of young children, usually occurring within a few months of the primary infection (Miller, Seal, and Taylor, 1963). It may also be a terminal event in other forms of tuberculosis. Though predominantly a disease of the young, a considerable number of cases arising in patients over the age of 60 years has been described (Braun, 1917 ; Hartwich, 1922).

With modern public health measures, including mass miniature radiography, particularly of high-risk groups, B.C.G. vaccination, and effective chemotherapy for active disease, the reservoir of tuberculous infection in many countries has diminished considerably. The incidence of classical miliary tuberculosis has fallen simultaneously and this disease is now rare even in the age group that was formerly most susceptible.

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Over recent years disturbing reports have been published of the diagnosis of disseminated tuberculosis being made at necropsy, the disease not having been suspected during life (Treip and Meyers, 1959 ; Böttiger, Nordenstam, and Wester, 1962 ; Oswald, 1963 ; Brunner and Haemmerli, 1964). This type of tuberculosis which we shall refer to as "cryptic" does not present the clinical and radiographic features associated with classical miliary tuberculosis.

The object of this paper is to present our experience of this type of tuberculosis with a view to increasing awareness of its existence. These patients will be compared with others suffering from classical or overt miliary tuberculosis in order to emphasize that they constitute a separate clinical entity.

The Patients

The case records of 40 adults diagnosed in Edinburgh between 1954 and 1967 as having disseminated tuberculosis were studied. The series comprised 16 males and 24 females aged 21–89 years. Only three patients were not of British extraction, two being European and one Indian.

A total of 24 cases were classified as having overt disseminated tuberculosis and 16 as having the cryptic variety. With one exception all cryptic cases were diagnosed between 1962 and 1967.

Clinical Features

The sex and age distribution in both groups is shown in Table I.

TABLE I.—*Age and Sex Distribution of 40 Adults Suffering from Miliary Tuberculosis*

Age (Years)	Overt		Cryptic	
	M	F	M	F
20–29	1	5		
30–39		2	1	1
40–49	2		2	
50–59	2			1
60–69	1	1	1	1
70–79	2	5	2	4
80–89	1	2	1	2

A past or contact history of tuberculosis was obtained from eight patients in the overt group and from four in the cryptic group. At the time of diagnosis 13 patients in the overt group and 10 patients in the cryptic group had concomitant illnesses. Of these 23 patients 15 were over the age of 60 years.

Patients estimated the duration of their illnesses before admission to hospital from a few days to three years. In about half the cases symptoms had been present for no more than three months, and in only 15% did the duration of symptoms exceed nine months.

General malaise, loss of weight, and respiratory symptoms were found in 78%, 75%, and 18% of patients respectively. These symptoms were as common in patients with cryptic disseminated tuberculosis as in those with overt miliary disease. Less common symptoms were night sweats (seven patients) and abdominal pain (five patients). Haemoptysis was a feature in four cases, but two of these patients had pulmonary infarcts and another a simple pneumonia. Five patients had prominent urinary symptoms. These were explained by renal tuberculosis in two cases, acute pyelonephritis in one, and a hypernephroma in another. The fifth patient had undergone a nephrectomy several years before for undiscovered reasons, and her urinary symptoms did not respond to antituberculosis drugs.

In the 24 patients with classical miliary tuberculosis choroidal tubercles were found in five, enlarged lymph nodes in three, and signs of meningitis in four. None of these features was present in patients with the cryptic variety. Splenomegaly was found in two patients in each group. The liver was enlarged in five overt cases and in three cryptic cases.

Fever, usually of the intermittent type, was present in 19 overt cases and in 14 patients in the cryptic group. In 10 patients with cryptic disseminated tuberculosis, pyrexia which remained unexplained despite prolonged and intensive hospital investigation constituted the diagnostic problem.

The chest radiograph abnormalities are shown in Table II. Whereas three-quarters of the patients with overt disseminated tuberculosis had miliary mottling on the chest radiograph this was present in only one out of the 16 with cryptic disease, and this patient was known to have industrial lung disease. Over half the patients in the latter group had normal chest radiographs compared with only 4 out of 25 with overt miliary tuberculosis.

TABLE II.—*Chest Radiograph Abnormalities*

	Overt	Cryptic
Normal	3	9
Miliary mottling	14	1*
Miliary + pulmonary	4	0
Miliary + effusion	1	0
Pulmonary	1	3
Pleural effusion	1	0
Simple pneumonia	0	3
Total	24	16

* This patient was known to have industrial lung disease.

For various reasons the results of tuberculin tests were available for only 15 patients with overt miliary tuberculosis and 10 with the cryptic variety. Only three patients in the first group had negative tuberculin tests initially, but these were not repeated. Four patients with cryptic disseminated tuberculosis had negative skin tests initially; two of these remained negative and two became positive over the course of the illness.

Haematological Findings

The specific blood disorders found in the series are shown in Table III. There was no difference in the incidence of neutropenia and monocytosis in the two groups of patients. Pancytopenia and leukaemoid reactions were more common with cryptic miliary tuberculosis.

TABLE III.—*Specific Blood Disorders in Disseminated Tuberculosis*

	Overt	Cryptic
Neutropenia*	3	2
Monocytosis†	2	1
Pancytopenia	1	2
Leukaemoid reaction	0	1
Others	1 thrombocytopenia. 1 acquired haemolytic anaemia	1 myeloma-like marrow picture

* Neutropenia <2,500 per cu.mm. † Monocytosis >800 per cu.mm. (Dacie and Lewis, 1963).

The erythrocyte sedimentation rate (E.S.R.) was recorded in 39 cases, the values being shown in Table IV. Only three patients with overt miliary tuberculosis (13%) had an E.S.R. of greater than 50 mm. in one hour compared with 9 out of 16 (56%) patients with the cryptic form.

TABLE IV.—*Erythrocyte Sedimentation Rate (Westergren) in Disseminated Tuberculosis*

E.S.R. (mm. in 1 hour)	Overt	Cryptic
<10	2	1
10–49	18	6
50–99	3	5
100+	0	4
Total	23	16

Method of Diagnosis

The method of diagnosis of miliary tuberculosis in both groups of patients is shown in Table V. In many with overt miliary tuberculosis the diagnosis was suggested soon after admission to hospital either by the presence of choroidal tubercles or miliary mottling on the chest radiograph or by the results of examination of cerebrospinal fluid in those with meningitis. Tubercle bacilli were cultured from sputum, urine, or cerebrospinal fluid in 18 of the 20 patients diagnosed by clinical and radiographic means. Necropsy confirmation of the diagnosis was obtained in one other.

TABLE V.—*Method of Diagnosis of Disseminated Tuberculosis*

	Overt	Cryptic
Clinical (physical examination, chest radiograph appearance)	20	0
Operation	3	2
Liver biopsy	0	1
Necropsy	1	3
Therapeutic trial with PAS and isoniazid	0	10
Total	24	16

In the cryptic group disseminated tuberculosis was first diagnosed at necropsy in three cases. Only in one of these was the correct diagnosis suspected before death. In 10 other patients the diagnosis of cryptic disseminated tuberculosis was made on the response to a therapeutic trial with para-aminosalicylic acid (PAS) and isoniazid.

Tubercle bacilli were ultimately cultured from the sputum or urine of five patients in the cryptic group.

Results of Treatment

A total of 30 patients (75%) survived. The mortality was the same in both groups (25%). Two patients in each group died untreated. Only one of these was suspected of having tuberculosis before death. The advanced ages of the patients and the short duration of antituberculosis therapy in those treated before death is apparent from Table VI. The high incidence of coincident disease is also notable.

Of patients treated with antituberculosis drugs the temperature returned to normal within one week in six cryptic cases compared with only three overt cases. Fourteen of the latter required at least two weeks and usually longer for the temperature to return to normal.

Three patients with overt disseminated tuberculosis and six with the cryptic variety had hypersensitivity reactions to PAS or streptomycin. In three instances the reaction was to PAS alone and in five to both drugs. One patient had a blood

eosinophilia of 76% as the only manifestation of hypersensitivity to PAS.

TABLE VI.—*Causes of Death, Duration of Antituberculosis Chemotherapy, and Presence of Other Diseases in 10 Patients with Disseminated Tuberculosis*

Group	Sex	Age (years)	Cause of Death	Other Disease	Duration of Therapy Before Death
Cryptic	M	77	Klebsiella pneumonia	None	2½ months
	M	83	Miliary tuberculosis	? Ulcerative colitis. Receiving corticosteroids	None
	M	61	Miliary tuberculosis	Subdural haematoma. Electrolyte imbalance	16 days
	F	72	Miliary tuberculosis	Pancytopenia. Receiving corticosteroids	None
Overt	F	71	Uraemia	Chronic pyelonephritis. Metastatic breast carcinoma	7 days
	F	86	Miliary tuberculosis	Tuberculous meningitis	6 days
	M	72	Massive gastrointestinal haemorrhage	Gastric ulcer. Emphysema	9 days
	F	89	Bronchopneumonia	Pancytopenia	2 months
	M	86	Miliary tuberculosis	None	None
	F	79	Cerebrovascular accident	Deep venous thrombosis. Pulmonary infarction	None

Discussion

Disseminated tuberculosis is no longer a major cause of death in many countries, but the fact that effective treatment is available makes it important to reach the correct diagnosis as soon as possible.

The peak age incidence of this form of the disease has increased steadily over the last 45 years (Hartwich, 1922; Chapman and Whorton, 1946; Biehl, 1958) and was in the eighth decade in the present series. Fifty-eight per cent. of the patients were over the age of 60 years. The reason for this change is not fully understood. Though natural primary tuberculosis and its complications are now acquired at a much later age (Barrett-Connor, 1967), the majority of the very elderly in this series are likely to have been infected early in life. Nevertheless, the allergic response to the tubercle bacillus, as measured by skin tuberculin sensitivity, declines after the age of 50 years (Johnston, Ritchie, and Murray, 1963) and it therefore seems possible that disseminated tuberculosis in the elderly may be due to the breakdown of old tuberculous foci in debilitated patients with waning immunological mechanisms.

A cryptic form of disseminated tuberculosis has emerged and it differs in many respects from classical miliary tuberculosis. It was most often found in patients, particularly women, over the age of 60 years, when it was as common as overt miliary tuberculosis.

Cryptic disseminated tuberculosis is characterized by an insidious onset and progression which unobtrusively undermines general health but may not arouse the patient's concern until an advanced stage is reached. Physical examination reveals an ill, exhausted individual with severe systemic upset. Pyrexia is not invariable, but when present is commonly intermittent and unspectacular. Choroidal tubercles were not found in the cryptic type of miliary disease.

Miliary mottling in the chest radiograph, an important clue to the diagnosis of disseminated tuberculosis, was found in 19 out of 24 overt cases in the series, but was present in only 1 of the 16 patients in the cryptic group, and he was known to have industrial lung disease. Böttiger *et al.* (1962) reported five fatal cases of disseminated tuberculosis; none had miliary mottling in the chest radiograph and the diagnosis was made only at necropsy.

Similarly the tuberculin test may be repeatedly negative, but in some cases the development of tuberculin sensitivity over the course of a few weeks provides an important diagnostic clue.

The difficulty of reaching a diagnosis of disseminated tuberculosis in the elderly in the absence of classical features is complicated further by the high incidence of concomitant disease processes. Treip and Meyers (1959) compared deaths from tuberculosis in a general hospital in two consecutive five-year periods, and though the overall incidence of disseminated tuberculosis was reduced in the second period 75% of cases were undiagnosed before necropsy compared with less than one-third of cases during the first five years. Brunner and Haemmerli (1964) reported 24 cases of miliary tuberculosis; 12 patients died and in only one of these was the diagnosis suspected before death. The large number of missed diagnoses was partly explained by the advanced age of the patients, the advanced stage of the disease, and the high incidence of other fatal lesions. Many patients died within a few days of admission to hospital and would have been unable to benefit from antituberculosis chemotherapy even if the correct diagnosis had been made. Our data (Table VI) strongly support these conclusions; of the 10 deaths only five could be directly attributed to tuberculosis, and in two of these the disease was unsuspected during life.

The association of blood disorders with tuberculosis has been debated for many years and has been reviewed by Lowther (1959), Oswald (1963), and Corr, Kyle, and Bowie (1964).

Neutropenia and monocytosis occur with equal frequency in overt and cryptic disseminated tuberculosis (Table III), but other blood disorders were found in 3 out of 16 cryptic cases compared with only 1 out of 24 with overt disease.

Pancytopenia complicating tuberculosis has been reported by Fountain (1954), Medd and Hayhoe (1955), and Dawborn and Cowling (1961) and more recently in association with disseminated atypical mycobacterial infection (Zamorano and Tompsett, 1968). Leukaemoid reactions (Twomey and Leavell, 1965), myelofibrosis (Crail, Alt, and Nadler, 1948), and polycythaemia (Fitzpatrick and Schwartz, 1949; Guild and Robson, 1950) have also been associated. It is generally agreed that bizarre blood disorders are particularly likely to be associated with areactive disseminated tuberculosis (O'Brien, 1954; Oswald, 1963; Rodin and Hnatko, 1963), which does not present the features of classical miliary tuberculosis and is more likely to be a cryptic disease first diagnosed at necropsy. The 68 cases of miliary tuberculosis reported by Biehl (1958) were mainly of the overt type; no unusual blood disorders were found.

Successful treatment of tuberculosis had no effect on the blood picture of those patients with pancytopenia (Oswald, 1963), myeloproliferative disorders, and others with leukaemia and tuberculosis (Corr *et al.*, 1964). Unfortunately the possibility of underlying tuberculosis in patients with leukaemia is not widely realized during life, and the administration of corticosteroids and antimitotic agents facilitates the spread of tuberculosis or reactivates quiescent foci with fatal consequences (Iversen and Ofstad, 1960; Böttiger *et al.*, 1962). The simultaneous use of antituberculosis drugs when treating pancytopenia, leukaemia, and other blood dyscrasias has therefore been advocated (Medd and Hayhoe, 1955; Rosenthal, 1956; Skårberg, Lagerlöf, and Reizenstein, 1967).

In the present series as many as 10 of the 16 patients with cryptic disseminated tuberculosis presented with pyrexia of unknown origin as the diagnostic problem. No cause may be found despite prolonged and intensive hospital investigations, but such a problem, particularly if it arises in an elderly woman or in association with a blood dyscrasia, should alert the physician to the possibility of cryptic disseminated tuberculosis. The importance of tuberculosis, particularly disseminated tuberculosis, as a cause of fever of unknown origin has been emphasized (Böttiger, 1957; Petersdorf and Beeson, 1961; Böttiger *et al.*, 1962).

The problem of making a firm diagnosis remains once the suspicion has been raised. The absence of typical clinical and radiographic features has already been discussed. In the early stages and even later the tuberculin test may be misleading.

Brunner and Haemmerli (1964) showed that liver biopsy was a valuable diagnostic investigation in miliary tuberculosis, with positive biopsies in 75% of 163 cases collected from the literature. In the present series liver biopsy was attempted in three patients with cryptic miliary tuberculosis and gave the diagnosis in one only.

Histological examination of bone marrow and culture for tubercle bacilli has been shown to increase the number of diagnoses in miliary tuberculosis in children (Emery and Gibbs, 1954); in only one out of four overt and three cryptic cases in our series was a positive culture obtained.

When all investigations fail to determine the cause of pyrexia the only method by which a diagnosis of cryptic miliary tuberculosis can be proved or refuted during life is to observe the response to a therapeutic trial with PAS and isoniazid. Streptomycin is not given because it would influence other bacterial infections. The clinical features in these cases are so striking in their seriousness that when improvement on chemotherapy takes place there is no doubt about its occurrence.

The criteria by which progress during antituberculosis therapy is assessed are of paramount importance. In 6 out of 10 patients diagnosed by means of a therapeutic trial the temperature fell to normal within a week of starting treatment. Improved well-being was usually obvious within two to six weeks, when gain in weight also became apparent. An important rise in haemoglobin was usually demonstrable within four to six weeks. Petersdorf and Beeson (1961) also found the response to antituberculosis drugs a useful diagnostic test in cases of pyrexia of unknown origin. They concluded that "when the condition of the patient will not allow liver biopsy to be done, or if this and other diagnostic manœuvres fail, a therapeutic trial with antituberculous drugs is indicated." Such a trial was also advocated by Cleve, Young, and Vicente-Mastellari (1957). We wholeheartedly support this view.

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Role of Acidosis in Renal Osteomalacia

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Summary: Of nine patients with uraemic osteomalacia, the underlying renal lesion was pyelonephritis in seven. All of the patients were characterized by impairment of acidifying power and severe metabolic acidosis. It is suggested that metabolic acidosis may be a definite factor in the pathogenesis of uraemic osteomalacia, possibly by reducing the proportion of trivalent phosphate in the plasma and/or by reducing plasma calcium.

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Introduction

Osteomalacia and rickets are seen in two main types of acidotic renal disease, which were effectively separated by Albright and Reifenstein (1948). In the first type (renal tubular acidosis) the metabolic acidosis is due to the tubular acidifying defect and is not associated with general (glomerular) renal failure. This type of renal osteomalacia is characterized by severe hypophosphataemia.

The second type of renal osteomalacia is that which occurs in some cases of general renal failure. This bone disease forms part of the spectrum that Stanbury (1967, 1968) calls azotaemic